IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of	Conf. No.: 4888
EDENS et al	Atty. Ref.: LCM-4662-157
Serial No. 10/572,811	TC/A.U.: 1657
Filed: March 22, 2006	Examiner: S.K. Singh

For: USE OF PROLINE SPECIFIC ENDOPROTEASES TO HYDROLYSE PEPTIDES AND PROTEINS

* *

April 1, 2011

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

Appellant hereby **appeals** to the Board of Patent Appeals and Interferences from the last decision of the Examiner.

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(I) REAL PARTY IN INTEREST

The real party in interest is DSM IP Assets, a corporation of The Netherlands.

(II) RELATED APPEALS AND INTERFERENCES

The appellant, the undersigned, and the assignee are not aware of any related appeals, interferences, or judicial proceedings (past or present), which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

(III) STATUS OF CLAIMS

Claims 9, 11, 12 and 23-31 are pending and have been rejected. No claims have been substantively allowed. Claims 1-8, 10 and 13-22 are canceled. Claims 9, 11, 12 and 23-31 are appealed.

In the Advisory Action mailed January 20, 2011, dependent claims 25 and 26 are objected to as dependent on a canceled claim. As this objection is not appealable, this informality will be dealt with after the appeal has been heard on the merits.

(IV) STATUS OF AMENDMENTS

Amendments have been filed since the date of the Final Rejection, the Amendment dated January 3, 2011.

(IV) SUMMARY OF CLAIMED SUBJECT MATTER

The invention of independent claim 9 claims a method of using a proline specific endoprotease to hydrolyse at a pH of below 5.5, proline rich peptides which are brought with celiac disease, a disease associated with the occurrence of celiac disease, or a disease caused by a decreased level in a patient's body of proline specific proteases required for breakdown of these peptides, by administering a dietary supplement or a medicament comprised of the proline specific endoprotease for ingestion by a patient in need thereof, whereby the proline specific endoprotease is active in the stomach and is pepsin resistant (specification, page 8, line 34, page 9, beginning at line 18, page 12 beginning at line 6, page 15, line 29 to page 16, line 4; and Example 8 demonstrating that *A. niger* proline–specific endoprotease is capable of breaking down proteins in the stomach).

The invention of independent claim 11 claims a method of using a proline specific endoprotease having a pH optimum below 6.5 (specification, page 8, line 2), by administering the proline specific endoprotease for ingestion by a patient in need thereof, whereby the patient suffers from celiac disease, a disease associated with the occurrence of celiac disease, or a disease caused by a decreased level in the patient's body of proline specific proteases, and whereby the proline specific endoprotease is active in the stomach and is pepsin resistant (specification, page 7, lines 17-22, page 8, lines 1-5, page 8, line 34, page 9, beginning at line 18, page 12 beginning at line 6, page 15, line 29 to page 16, line 4; and Example 8 demonstrating that *A. niger* proline–specific endoprotease is capable of breaking down proteins in the stomach).

(V) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The sole ground of rejection to be reviewed on appeal is that of obviousness of claims 9-12 and 23-31 over Messer *et al.* (1976) (Messer) in view of Hausch *et al.* (2002) (Hausch) and Dekker *et al.* (WO 02/45 524 A2) (Dekker).

(VI) ARGUMENT

The invention provides a method of using a proline specific endoprotease to hydrolyse at a pH of below 5.5, proline rich peptides which are associated with celiac disease, a disease associated with the occurrence of celiac disease, or a disease caused by a decreased level in a patient's body of proline specific proteases required for breakdown of these peptides. The claimed method comprises administering a dietary supplement or a medicament comprised of the proline specific endoprotease for ingestion by a patient in need thereof, whereby the proline specific endoprotease is active in the stomach and is pepsin resistant.

The specification (page 8, lines 26-32) provides a discussion as to how the prior art has attempted to provide solutions for activity in humans. In particular, it was necessary to break down gluten in the gut rather than the stomach because the prior art enzyme is not active under acidic conditions and is destroyed in the stomach because it possesses a neutral pH optimum, implying instability under acidic conditions of the stomach. The prior art therefore attempted to solve the problem by employing a coating for the enzyme.

Messer discloses (first sentence of the 3rd paragraph) that the four enzymes discussed in the paper should act "within the small intestine" (emphasis added). In the next paragraph, Messer discloses that the patient used "enteric-coated" (emphasis added) tablets of crude papain. The term "enteric-coated" means that tablet is acid-protected by a special coating which disappears once the tablet has traveled past the stomach. Messer, therefore, clearly leads **away** from the invention as claimed which requires that the proline specific endoprotease is active in the stomach.

Hausch refers to the breakdown of gliadin peptides in the brush-border membrane (BBM - located in the **intestinal** wall) by exo and endopeptidase (Hausch, page G997, left column, lines 13-16). Ordinarily, gliadin oligopeptides are broken down by peptidases located in the BBM of the intestinal enterocytes (Hausch, page G996, right column, last 2 lines from the bottom). BBM derived from human adult intestinal biopsy was used to verify this theory (Hausch, page G997, left column, lines 18-13 from the bottom). The conclusion is reached that:

> "Although PEP is expressed in human brain, lung, kidney and intestine, no such activity has been reported in the BBM to our knowledge." (Hausch, page G1002 left column, line 34)

Based on this, the suggestion is made:

> "Therefore, we suggest that supplementation of the celiac diet with bioavailable PEP….may be useful in attenuating or perhaps even eliminating the inflammatory response to gluten." (Hausch, page G1002, left hand column, line 37).

Hausch thus suggests use of PEP for breakdown of these gliadin peptides in the BBM or in the intestine. Hausch, therefore, like Messer, leads **away** from the claimed invention which requires that the proline specific endoprotease is active in the stomach.

The corresponding patent application of Hausch *et al.* (WO03/068170) further confirms this point. Hausch '170 mentions enteric formulations with an enteric coating (page 3, line 1 and lines 7-14), and further states that the glutenase should be stabilized to resist the digestion of the stomach (page 3, lines 3-5). The intention of this coating is to deliver the enzyme to the intestine. Thus, Hausch states:

> "Such formulations include formulations in which the glutenase is contained within an enteric coating that allows delivery of the active agent

> to the intestine and formulations in which the active agents are stabilized to resist digestion in acidic stomach conditions." (Hausch, page 3, lines 11-14).

Hausch clearly leads away from the claimed invention.

Dekker is relied upon for an alleged disclosure of an enzyme (a prolyl endoprotease) that can hydrolyze proline-rich peptides that are associated with celiac disease at a pH of below 5.5, or that has a p11 optimum below 6.5. However, Dekker describes the use of proline specific endoprotease *in vitro* rather than *in vivo*. While reference is made to reducing allergenicity of food (Dekker, page 7 lines 28-32), the enzyme is incubated with the food proteins prior to consumption. It would appear that enzymes used in this way are killed off during food preparation rather than during food digestion. Dekker is irrelevant to the method as claimed.

Based on the above, it is clear that one of ordinary skill, as of the filing date of the present case, would not have been motivated to rely on Messer and/or Hausch as both of those references focus on the intestine and lead **away** from the method as claimed. Dekker is irrelevant for the reasons discussed above. The cited art, taken singly or in combination, thus does not give rise to a *prima facie* case of obviousness.

As yet further evidence of patentability of the claimed invention, attention is drawn to results described in two articles in well-known scientific publications. These are Stepniak *et al.* published in *Am. J. Physiol. Gastrointest. Liver Physiol.* (Stepniak) and Mitea *et al.*, published in *Gut* (Mitea). Luppo Edens is named as a co-author on both publications. Stepniak and Mitea were submitted with the Amendment dated June 14, 2010.

Stepniak describes highly efficient gluten degradation using the *Aspergillus niger* proline specific endoprotease. Mitea demonstrates the efficacy of the enzyme (AN-PEP) towards destroying the toxic gluten epitopes in a validated dynamic system closely matching the human gastrointestinal tract (TIM system). In the latter test, a slice of bread as well as a whole fast food menu were introduced into the dynamic system (Mitea, page 25, left hand column, Abstract). These results demonstrate unexpected benefits arising out of the invention as presently claimed.

The proline specific endoprotease ("PEP") employed in the present invention is pepsin resistant. This feature is recited in the claims. Moreover, Stepniak shows that the present prolyl endoprotease is highly effective in the stomach compared to the prolyl endoprotease used by Hausch. Hausch uses *Flavobacterium meningosepticum* prolyl oligopeptidase which is not active in the acid pH range (see Figure 1 on page G623), but this *Flavobacterium meningosepticum* prolyl oligopeptidase is also not resistant against pepsin (see Figure 1, page G623).

This showing clearly evidences a surprising and unexpected property relating to pepsin sensitivity. In view of this, it is believed that the invention as claimed is not suggested by Messer, Hausch and/or Dekker, whether taken singly or in any combination. Reversal of the obviousness rejection is respectfully requested.

CONCLUSION

It is believed that the application is in clear condition for allowance. Early reversal of the final rejection and passage of the subject application to issue are earnestly solicited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /Leonard C. Mitchard/
Leonard C. Mitchard
Reg. No. 29,009

LCM:lff
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

(VII) CLAIMS APPENDIX

9. A method of using a proline specific endoprotease to hydrolyse at a pH of below 5.5, proline rich peptides which are brought with celiac disease, a disease associated with the occurrence of celiac disease, or a disease caused by a decreased level in a patient's body of proline specific proteases required for breakdown of these peptides, the method comprising administering a dietary supplement or a medicament comprised of said proline specific endoprotease for ingestion by a patient in need thereof, whereby the proline specific endoprotease is active in the stomach and is pepsin resistant.

11. A method of using a proline specific endoprotease having a pH optimum below 6.5, the method comprising administering said proline specific endoprotease for ingestion by a patient in need thereof, whereby the patient suffers from celiac disease, a disease associated with the occurrence of celiac disease, or a disease caused by a decreased level in the patient's body of proline specific proteases, and whereby the proline specific endoprotease is active in the stomach and is pepsin resistant.

12. The method according to claim 11, wherein the proline specific endoprotease is an *Aspergillus* enzyme.

23. The method according to claim 9, wherein the proline specific endoprotease is an *Aspergillus* enzyme.

24. The method according to claim 9, wherein the proline specific endoprotease is an *Aspergillus niger* enzyme.

25. The method according to claim 9, wherein the proline specific endoprotease is an *Aspergillus* enzyme.

26. The method according to claim 9, wherein the proline specific endoprotease is an *Aspergillus niger* enzyme.

27. The method according to claim 11, wherein the proline specific endoprotease is an *Aspergillus niger* enzyme.

28. The method according to claim 9, wherein the patient suffers from celiac disease.

29. The method according to claim 11, wherein the patient suffers from celiac disease.

30. The method according to claim 9, wherein the patient is gluten sensitive.

31. The method according to claim 11, wherein the patient is gluten sensitive.

(VIII) EVIDENCE APPENDIX

None.

(IX) RELATED PROCEEDINGS APPENDIX

None.